UNIVERSITI PUTRA MALAYSIA

SERUM AND URINE BIOMARKERS EXPRESSION (PLA2R-AG, ANTI-THSD7A AB AND RBP) IN DETERMINING ALTERNATIVE METHODS OF DIFFERENTIATING PRIMARY AND SECONDARY MEMBRANOUS GLOMERULONEPHRITIS

MAIFATA SADIQ MUAZU

FPSK(m) 2020 4

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By

MAIFATA SADIQ MUAZU

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

June 2020

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DEDICATION

This thesis is dedicated to my beloved parents Late Alhaji Mu'azu Maifata (may Allah have mercy on him) and Hajiya Maimuna Mu'azu Maifata, for their tireless support, motivation, parental guidance, encouragement and prayers.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

SERUM AND URINE BIOMARKERS EXPRESSION (PLA_2R-AG, ANTI-THSD7A AB AND RBP) IN DETERMINING ALTERNATIVE METHODS OF DIFFERENTIATING PRIMARY AND SECONDARY MEMBRANOUS GLOMERULONEPHRITIS

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Introduction: Differentiating primary from secondary membranous glomerulonephritis (MGN) using biomarkers is an important consideration in establishing its diagnosis and treatment strategies. Biomarkers are also important in prognosticating MGN cases to end-stage renal disease (ESRD). A biopsy is an invasive procedure. It cannot prove morphologically secondary MGNs whatever more than morphology can precede identification of its underlying cause. A biopsy is also not able to prognosticate MGN cases to ESRD. ***Objectives:*** This study aimed at providing an alternative method in differentiating primary and secondary MGN using serum and urine biomarkers (PLA_2R antigen (Ag) and anti-THSD7A antibodies (Ab)). It also aimed to demonstrate the importance of urine RBP as an effective biomarker for prognostication of MGNs to ESRD. ***Materials & Method:*** 125 patients were diagnosed with membranous glomerulonephritis (81 primary and 44 secondary MGN) from January 2012 to October 2019 in Hospital Serdang and Hospital Kuala Lumpur. Of this 125, only 69 were available and consented. Blood and urine samples were obtained for biomarkers analysis using enzyme-linked immunosorbent assay (ELISA) technique. ***Results:*** The proportion of primary and secondary MGN is 64.7% and 35.3% respectively. Both serum and urine PLA_2R-Ag are detected in seven primary MGN patients and one secondary MGN, having a strong positive correlation between serum and urine PLA_2R-Ag ($R= 0.932$, $p < 0.05$). There is a fair correlation of UPCr index with both serum ($R= 0.502$, $p < 0.001$) and urine ($R= 0.437$, $p < 0.001$) PLA_2R-Ag. Serum anti-THSD7A Ab was found positive in one primary MGN subject and four secondary MGN subjects. In contrast, none of the subjects shows any anti-THSD7A Ab detection in urine, and there is no correlation observed between serum and urine anti-THSD7A Abs ($R= 0.063$, $p = 0.604$). In addition, urine RBP showed statistically significant relationship with serum PLA_2R-Ag ($R= 0.239$, $p < 0.048$), eGFR ($R= -0.734$, $p < 0.001$) and UPCr index ($R= 0.235$, $p < 0.048$). ***Discussion &***

conclusion: Serum and urine PLA_2R-Ags alongside serum anti-THSD7A Ab could be used in prompt diagnosis and monitoring of primary MGN patients. In addition, urinary RBP and PLA_2R-Ag could also be utilised as important tools in treatment decisions and as prognostic indicators of primary MGN, thereby potentially able to prevent the progression to end-stage renal diseases (ESRD).

Keywords: Membranous glomerulonephritis, M-type phospholipase A_2 receptor (PLA_2R) Ag, anti-Thrombospondin domain-containing protein 7A (THSD7A) Ab, retinol-binding protein (RBP), Prognostication, End-stage renal disease (ESRD).

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

BIOMARKER SERUM DAN AIR KENCING (PLA_2R-AG, ANTI-THSD7A AB DAN RBP) DALAM MENENTUKAN KAEDAH ALTERNATIF UNTUK MEMBEZAKAN GLOMERULONEFRITIS MEMBRAN PRIMER DAN SEKUNDER

By

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Jun 2020

Pengerusi : Fauzah binti Abd Ghani (MBBS, MPATH)
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Pengenalan: Membezakan glomerulonefritis membran (MGN) primer dan sekunder menggunakan biomarker adalah penting untuk diagnosis dan rawatannya. Biomarker juga penting dalam mengandaikan kes-kes MGN yang akan berakhir dengan penyakit ginjal peringkat akhir (ESRD). Biopsi adalah satu prosedur invasif, malahan bagi MGN sekunder, biopsi tidak boleh membuktikan MGN sekunder secara morfologi dan juga morfologi boleh dilihat lebih awal daripada mengenalpasti sebab yang mendasarinya. Biopsi juga tidak dapat memberi gambaran tentang prognosis kes-kes MGN secara amnya kepada ESRD. ***Objektif:*** Kajian ini bertujuan untuk menyediakan kaedah alternatif dalam membezakan MGN primer dan sekunder dengan menggunakan biomarker serum dan urin (antigen PLA_2R dan antibodi anti-THSD7A). Ia juga bertujuan untuk menunjukkan pentingnya RBP urin sebagai biomarker yang tepat untuk mengandaikan prognosis MGN kepada ESRD. ***Bahan & Kaedah:*** 125 pesakit telah didiagnosis dengan MGN (81 primer dan 44 sekunder) dari Januari 2012 hingga Oktober 2019 di Hospital Serdang dan Hospital Kuala Lumpur. Daripada 125, hanya 69 subjek yang boleh dan bersetuju, yang terdiri daripada 30 MGN primer, 15 MGN sekunder MGN dan 24 subjek sihat telah bersetuju. Sampel darah dan air kencing telah diperolehi untuk analisis menggunakan teknik imunosorben berkait enzim (ELISA). ***Keputusan:*** Peratusan MGN primer dan sekunder masing-masing adalah 64.7% dan 35.3%. Kedua-dua antigen PLA_2Rserum dan urin dikesan dalam tujuh subjek MGN primer dan satu MGN sekunder, dan ini menunjukkan korelasi positif yang kuat di antara antigen PLA_2R serum dan urin ($R= 0.932$, $p < 0.05$). Terdapat korelasi antara indeks UPCr dengan kedua-dua serum ($R= 0.502$, $p < 0.001$) dan urin ($R= 0.437$, $p < 0.001$) antigen PLA_2R. Antibodi anti-THSD7A serum didapati positif dalam satu subjek MGN primer dan empat subjek MGN sekunder. Sebaliknya, tiada satupun subjek menunjukkan pengesanan antibodi anti-THSD7A dalam urin dan tidak ada korelasi yang diperhatikan antara serum dan urin antibodi anti-THSD7A (R=

0.063, p = 0.604). Di samping itu, RBP urin menunjukkan hubungan yang signifikan secara statistik dengan serum antigen PLA_2R (R= 0.239, p < 0.048), eGFR (R= -0.734, p < 0.001) dan indeks UPCr (R= 0.235, p < 0.048). ***Perbincangan & kesimpulan:*** Antigen PLA_2R serum dan urin bersama antibodi anti-THSD7A boleh digunakan dalam diagnosis dan pemantauan pesakit MGN primer. Di samping itu, RBP urin dan antigen PLA_2R urin, kedua-duanya boleh digunakan sebagai alat penting dalam menentukan bentuk perawatan dan juga boleh dijadikan penunjuk prognostik MGN primer, justeru berpotensi untuk mencegah daripada perkembangan MGN primer kepada ESRD.

Kata kunci: Glomerulonefritis membran, antigen M-jenis fosholipase A_2 penerima (PLA_2R), antibody anti-Thrombospondin domain-mengandungi protein 7A (THSD7A), protein terikat retinol (RBP), Prognostication, Penyakit renal peringkat akhir (ESRD).

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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

MGN:	Membranous Glomerulonephritis
PLA_2R Ag:	M-type Phospholipase A_2 receptor antigen
Anti-THSD7A Ab:	Anti-Thrombospondin type-1 domain-containing protein 7A antibody
RBP:	Retinol Binding Protein
UPCr Index:	Urine Protein Creatinine Index
eGFR:	Estimated Glomerular Filtration Rate
S.E:	Standard Error
COR:	Crude Odd Ratio
AOR:	Adjusted Odd Ratio
AUC:	Area Under the Curve
C. I:	Confidence Interval
GBM:	Glomerular Basement Membrane
IHC:	Immunohistochemistry
TMB:	3, 3, 5, 5, tetramethylbenzidine
KDIGO:	Kidney Disease Improving Global Outcome
NEP:	Neutral Endopeptidase
mg:	Milligram
mL:	Millilitre
mmol:	Millimole
μmol:	Micromole
ng/mL:	Nanogram/millilitre
pg/mL:	Picogram/millilitre
Ab:	Antibody
PCT:	Proximal convoluted tubule

HBV:	Hepatitis B Virus
HCV:	Hepatitis C Virus
DM:	Diabetes mellitus
LN:	Lupus nephritis
SLE:	Systemic Lupus Erythematosus
Ag:	Antigen
ESRD:	End-stage renal disease

CHAPTER 1

INTRODUCTION

1.1 Background

Membranous glomerulonephritis (MGN) is a form of the glomerular disease characterized by immune complex deposition within the subepithelial aspect of glomerular membrane and formation of perpendicular projections between the podocyte cytoplasm and glomerular basement membrane (GBM) (Larsen *et al.*, 2012).

Primary MGN is the most prevalent form of MGN found in 75-80%, while the remaining 20-25 % present as secondary to other conditions (Nasr *et al.,* 2009; Salant & Salant *et al.,* 2014; Cattran DC, 2017; William, 2017; Raza A, 2018). The most common cause of the adult nephrotic syndrome is MGN, which accounts for up to 20% of Hispanic and African American cases (Pierre & Debiec, 2015), responsible for 1.5-9% and 21-35% nephrotic syndrome in children and adults respectively (Kumar *et al.,* 2015). The incidence of MGN peaks in the fourth and fifth decades of life and appears higher in men than women (men: women is 2-3:1). The exact aetiology of MGN remains unclear, and the disease course varies significantly (Cattran & Brenchley, 2017).

Most patients present with asymptomatic proteinuria as the only clinical feature or abnormal urinalysis. Some patients present with microscopic haematuria whereas in few instances macroscopic haematuria may be part of the presenting features. Hypertension is seen when there is a renal compromise but can also be part of the feature in 30% of cases (Rosai, 2011).

According to the fifth study by the Malaysian Renal Biopsy Registry, the most common clinical presentation of primary MGN remained the nephrotic syndrome, seen in 75% of cases, followed by asymptomatic urine abnormality (13%), nephritic–nephrotic syndrome (4%) and nephritic syndrome in 4% of cases (Yahya *et al.*, 2014). The clinical and laboratory evaluation of primary and secondary MGN is the same. Therefore, a careful history, assessment of clinical findings, laboratory investigations and review of the histologic conclusions should be pursued to rule out secondary MGN (KDIGO, 2012).

It is essential to ascertain whether MGN is of primary or secondary type. In secondary MGN, the natural progression and the possible outcome of the disease depend on the underlying cause of the disease. The modality of treatment is by focusing on the underlying cause of the disease condition, which can lead to complete resolution. While in the case of primary MGN, the prognosis depends on the age at presentation, mean arterial blood pressure and the creatinine clearance at the time of presentation.

Unfortunately, these variables do not correlate with histopathological findings thus no extra information is given for prognostication (Beck & Salant, 2010).

About one-third of the patients may have complete remission from proteinuria; another one-third may experience partial remission while the remaining third may progress to end-stage kidney disease (MacTier *et al.,*1986; Donadio *et al.,* 1988; Polanco *et al.,* 2010; Cattran *et al.,* 2017).

1.2 Problem statement and justification

The clinical outcomes are complex and uncertain. Some patients with secondary MGN may have clinical features of MGN months or years before the underlying disease. Treatment with costly and potentially lethal medication is similarly difficult. Patients may undergo a series of renal biopsies to diagnose and control the condition of the disease. Therefore, the key to effective patient-centred care is to identify the exact type using reliable biomarkers for prompt diagnosis, treatment monitoring and prognostication while simultaneously reducing the rate of frequent biopsies.

Since the year 2000, significant achievements were recorded in the pathophysiology of MGN, with identification of neutral endopeptidase (NEP) in podocytes of neonates. This is followed by identification of M-type phospholipase A_2 receptor (PLA_2R), another podocyte antigen targeted by circulating antibodies and of recent, the discovery of thrombospondin type-1 domain-containing protein 7A (THSD7A) which is seen in a rare type of primary MGN.

Several techniques were proposed to differentiate primary and secondary MGN. This includes biopsy with ancillary immunohistochemical (IHC) study which stains positive for M-type Phospholipase A_2 receptor (PLA_2R) in primary MGN and in few variants of primary MGN, thrombospondin type-1 domain-containing 7A (THSD7A) could stain positive, thereby serving as a complementary test for serum anti-PLA_2R and serum anti-THSD7A Ab (Larsen *et al.,* 2016).

Although renal biopsy remains the bedrock in the MGN diagnosis, there is need to provide other alternatives using less and non-invasive methods in the form of serum and urine biomarkers respectively to differentiate primary and secondary MGN for prompt diagnosis, treatment and prognosis.

There have been attempts to use serum biomarkers for MGN like anti-PLA_2R and anti-THSD7A antibodies to differentiate primary from secondary MGN in few centres with very few attempts on urine biomarker anti-PLA_2R antibody (Ab) and no known attempt on urine anti-THSD7A Ab. Besides, most studies focused on the use of anti-PLA_2R Ab but no documented studies were found assessing serum and urine PLA_2R antigen (Ag). Therefore, there is a need to study the importance of serum and urine PLA_2R-Ag instead of anti-PLA_2R Ab to differentiate between primary and also to

detect the presence of anti-THSD7A in serum and urine of MGN patients for effective diagnosis.

End-stage renal disease is one of the possible complications of MGN. For this reason, retinol-binding protein (RBP), a marker of proximal tubular dysfunction, being a reliable biomarker for prognostication to end-stage renal diseases (ESRD).

This research aimed to analyse serum and urine biomarkers (PLA_2R-Ag and anti-THSD7A Ab) as possible biomarkers for MGN and provide an alternate tool for the differentiation of primary and secondary MGN.

1.3 Objectives

1.3.1 General Objective

To determine the role of serum and urine biomarkers expression in differentiating primary and secondary MGN.

1.3.2 Specific Objectives

a. To determine the sociodemographic and clinicopathological variables and predict factors associated with primary and secondary MGN.
b. To determine the performance of the biomarkers in diagnosing primary MGN.
c. To correlate between urinary RBP and established renal prognostic parameters.

1.3.3 Research hypothesis

a. Ho: Socio-demographic and clinicopathological variables may predict features of primary and secondary MGN.
b. Ho: Urinary RBP may correlate with renal prognostic parameter.

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